

# Cumulative Risk Assessment of Pesticides in the US

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# Background

- EPA defines cumulative risk as *"the risk of a common toxic effect associated with concurrent exposure by all relevant pathways and routes of exposure to a group of chemicals that share a **common mechanism of toxicity**."*
- The Office of Pesticide Programs (OPP) initially developed two guidance documents:
  - ***Guidance For Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity (USEPA, 1999)*** which describes the process for establishing common mechanism groups (CMGs);
  - ***Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity (USEPA, 2002)*** which describes the steps used in conducting CRA.



## Groups Analyzed using 1999/2002 Guidance

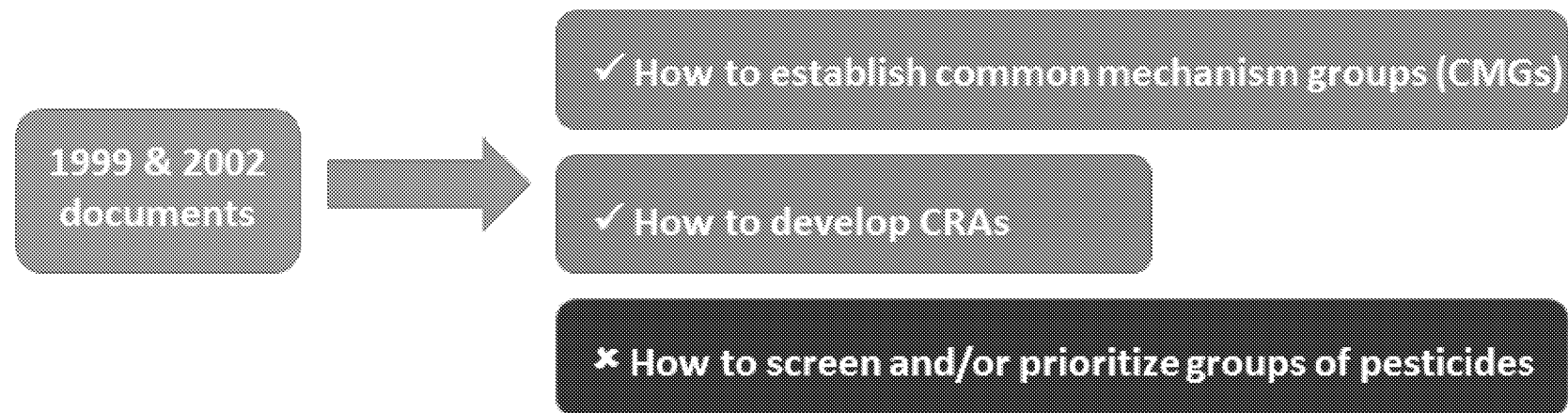
- N-methyl carbamates
- Organophosphates (OPs)
- Pyrethroids
- Triazines
- Chloroacetanilides

**EPA established  
CMGs**

- Dithiocarbamates (no CMG)
- Thiocarbamates (no CMG)



## Lessons Learned



- Also, establishing a CMG requires identification of the major steps leading to an adverse health effect following interaction of pesticides with their target
- This process requires large amounts of data and resources and is time-consuming

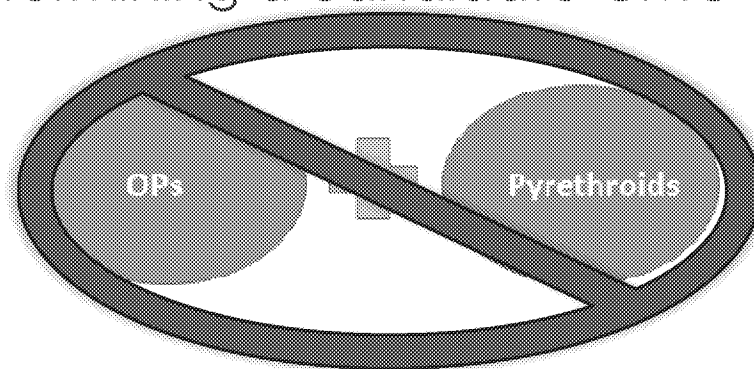
# Moving forward

- **A Screening Framework (FW) was developed in 2016 as a supplement to the current guidance documents**
  - ✓ Uses the same principles as the CMG guidance with respect to assessing available data.
  - ✓ Harmonizes terminology consistent with recent efforts by WHO.
  - ✓ Allows EPA to address statutory obligations while efficiently using resources.
  - ✓ Screens pesticides for **candidate** common mechanism groups (candidate CMGs) (pesticides with evidence of a common mechanism of toxicity).
  - ✓ Applies tiered approach to screen dietary, residential, and aggregate exposures.



## Pesticide Cumulative Risk Assessment: Screening & Prioritization Framework

- Shared chemical structure is not solely sufficient as support for a candidate CMG.
- In most cases, common apical outcome will not be used as the sole factor in determining a candidate CMG for screening purposes.

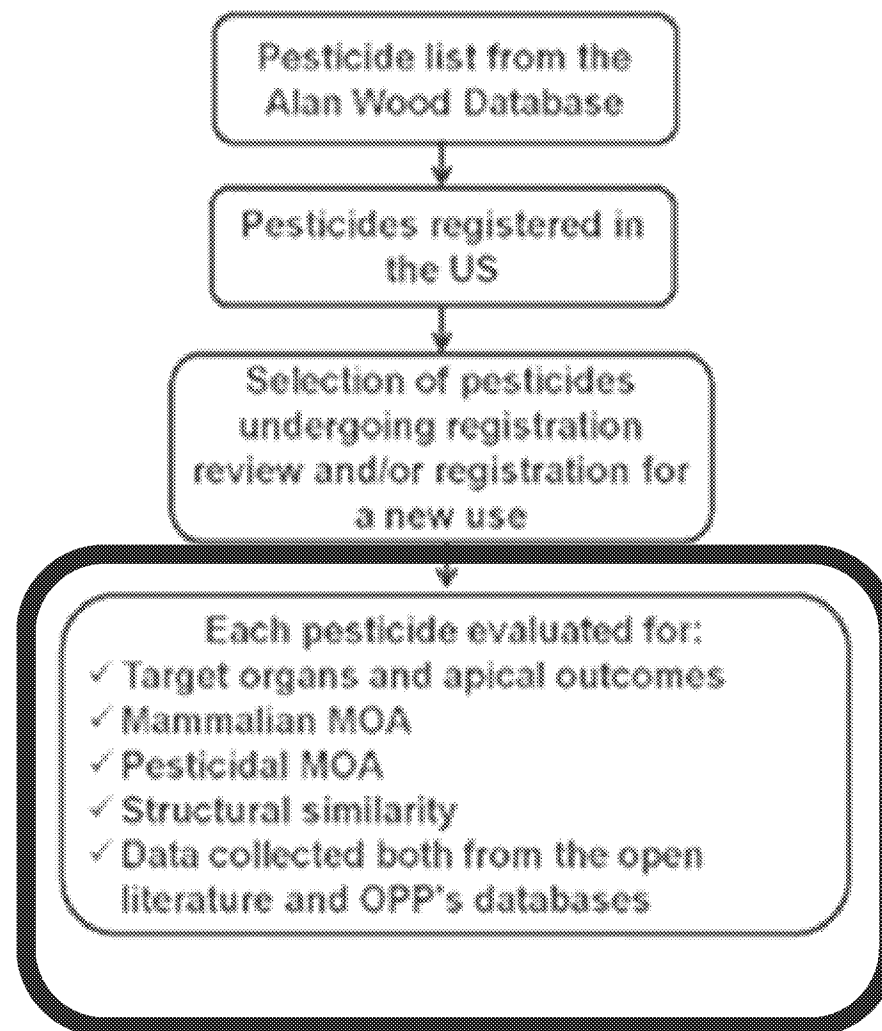


- Pesticidal MOA information is considered based on its relevance to humans
- Data & knowledge of mammalian MOA/AOP and pharmacokinetics provides the strongest information.



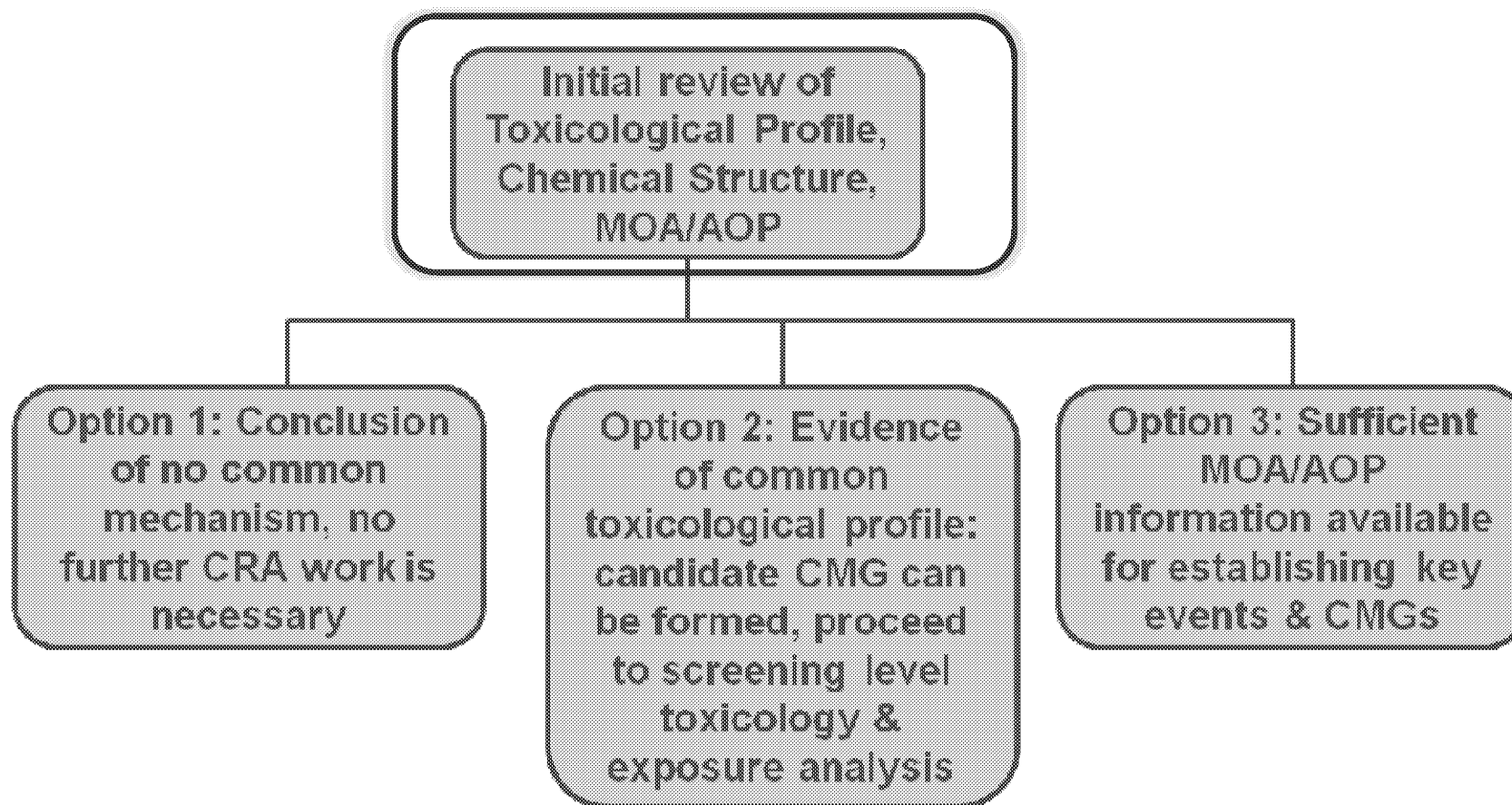
# Initial Prioritization and Review of Toxicological Information

**•Step 1 of screening framework: initial toxicological review**



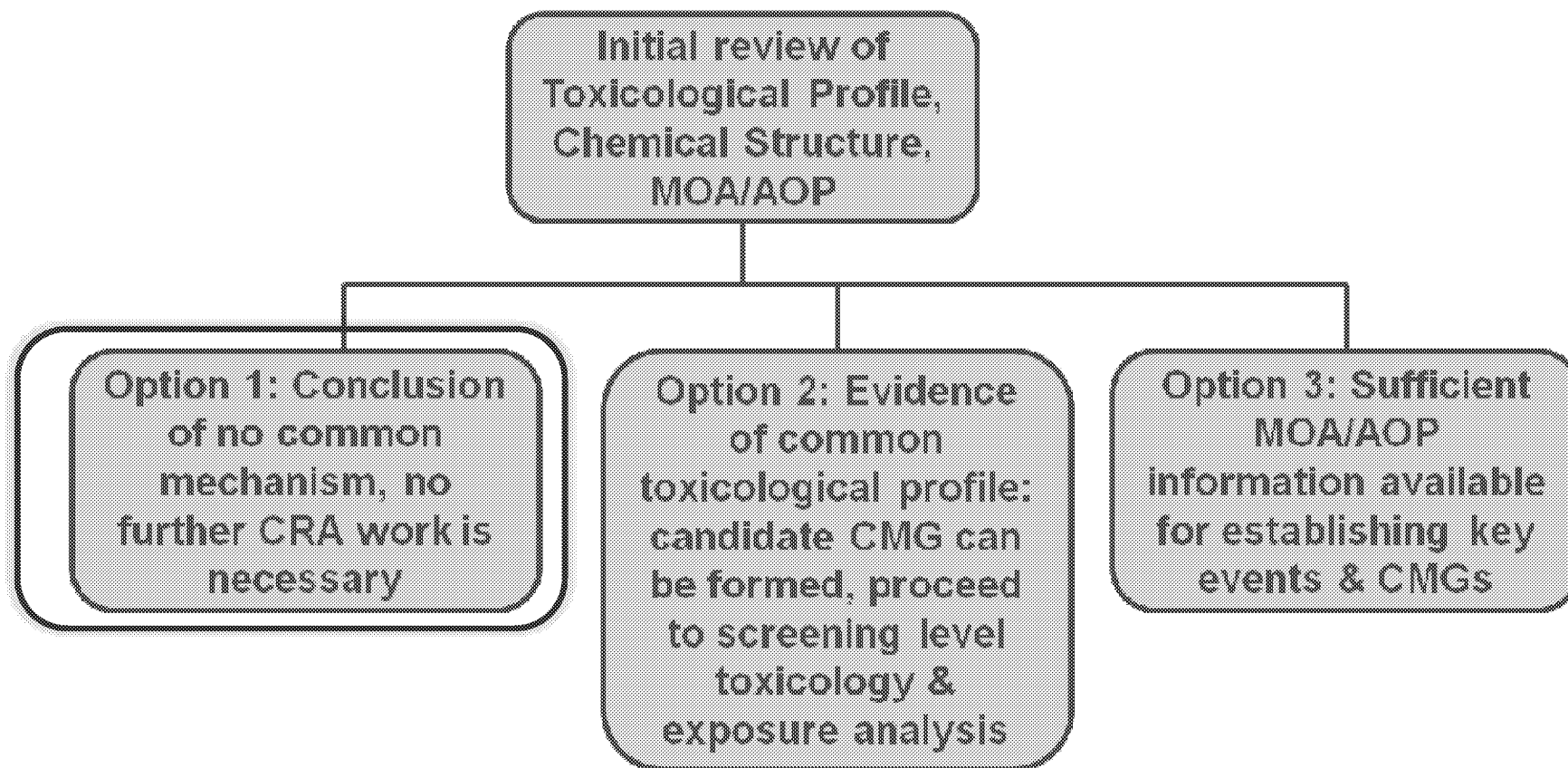


## Schematic for the CRA Screening FW





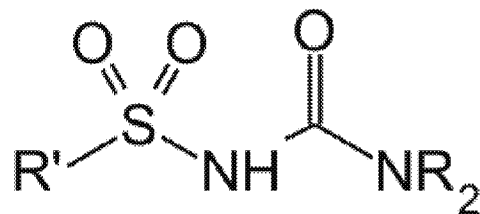
## Schematic for the CRA Screening FW





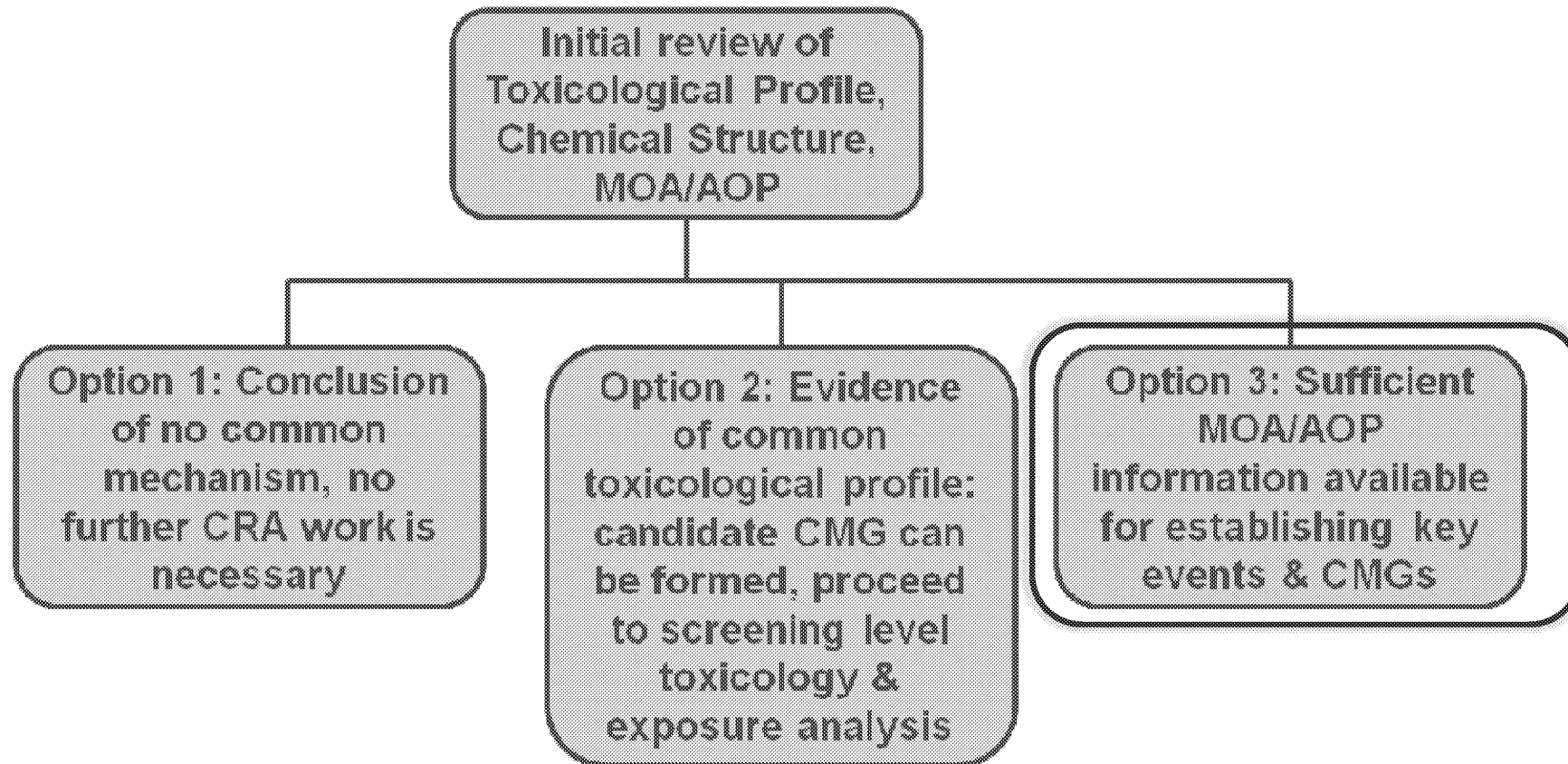
# Integration of Toxicological Screening Analysis Information

- *Option 1: Conclusion of **No Common Mechanism**, No Further CRA Work is Necessary:*
  - Pesticides do not share a similar toxicological profile.
  - Or, pesticides may share some chemical or toxicological characteristics (e.g., chemical structure or apical endpoint), but the toxicological database *does not support a testable hypothesis* for a common mechanism of action.
  - Example: sulfonylureas (e.g. prosulfuron, rimsulfuron)
    - Some structural similarity
    - Same pesticidal MOA (inhibition of acetolactate synthase)
    - No common mammalian target organ





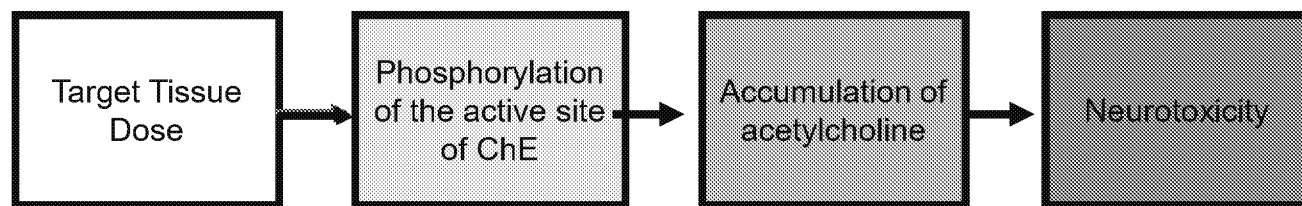
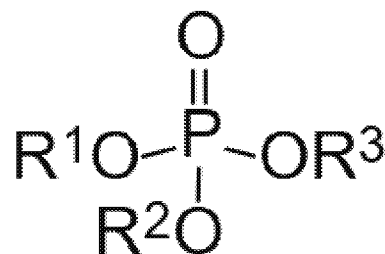
## Schematic for the CRA Screening FW





# Integration of Toxicological Screening Analysis Information

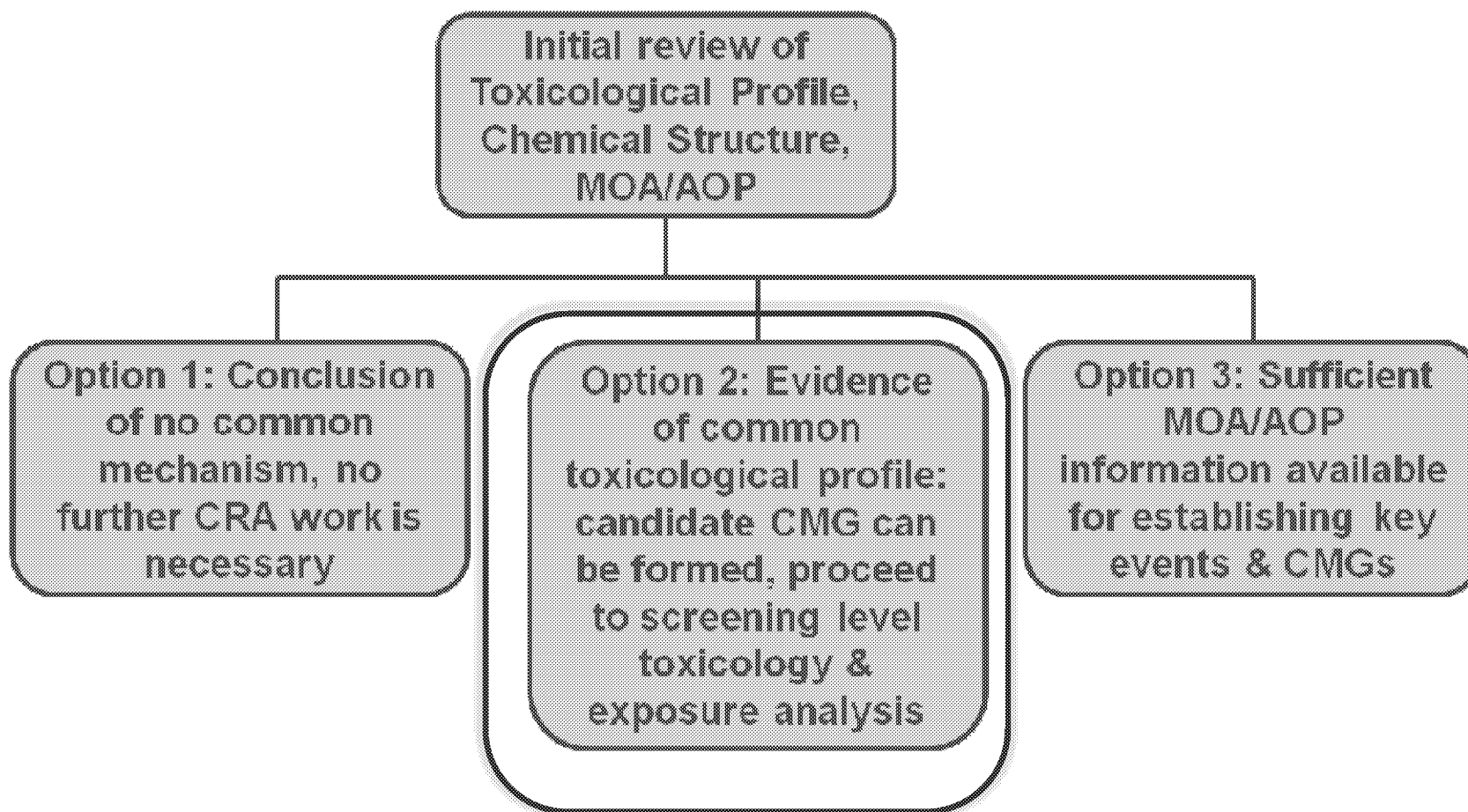
- *Option 3: **CMG can be established:** Sufficient mechanistic data are available to support establishing a set of key events in a pathway and thus support developing a science policy establishing a CMG.*
  - Example: organophosphates (e.g. malathion, tribufos)
    - Shared core structure
    - Key events in mammalian MOA established
    - A full CRA was conducted



MOA/AOP for organophosphates



## Schematic for the CRA Screening FW





# Integration of Toxicological Screening Analysis Information

- *Option 2: **Candidate CMG** can be formed; Screening-Level Exposure Analysis is Conducted:*
  - Candidate CMGs support a testable hypothesis for a common mechanism of action but do not have adequate data for establishing key events in a pathway as described in the MOA/AOP framework
  - Conduct a screening level dietary and/or residential exposure and aggregate analysis (tiered approach)
  - Example: anilinopyrimidines (cyprodinil, pyrimethanil)
    - High structural similarity
    - Shared pesticidal MOA (interfere with the biosynthesis of methionine and inhibit the secretion of hydrolytic fungal enzymes)
    - Shared mammalian *in vivo* effects ( liver necrosis, spongiosis hepatitis, decreased motor activity, hypothermia) and *in vitro* gene activation profile
    - No risks of concern identified in the screening assessment



## Groups analyzed with 2016 screening framework - final

Group	Chemicals	Candidate CMG	Outcome
Diacylhydrazines	methoxyfenozide, tebufenozide	Yes	Option 2: Screening-level CRA performed, no cumulative risk estimates of concern
Mectins	abamectin, emamectin	Yes	Option 2: Screening-level CRA performed, no cumulative risk estimates of concern
Triazolones	thiencarbazone, propoxycarbazone	No	Option 1: Conclusion of no common mechanism
Sulfonylureas	23 chemicals	No	Option 1: Conclusion of no common mechanism
Anilinopyrimidines	mepanipyrim, pyrimethanil, cyprodinil	Yes	Option 2: Screening-level CRA performed, no cumulative risk estimates of concern



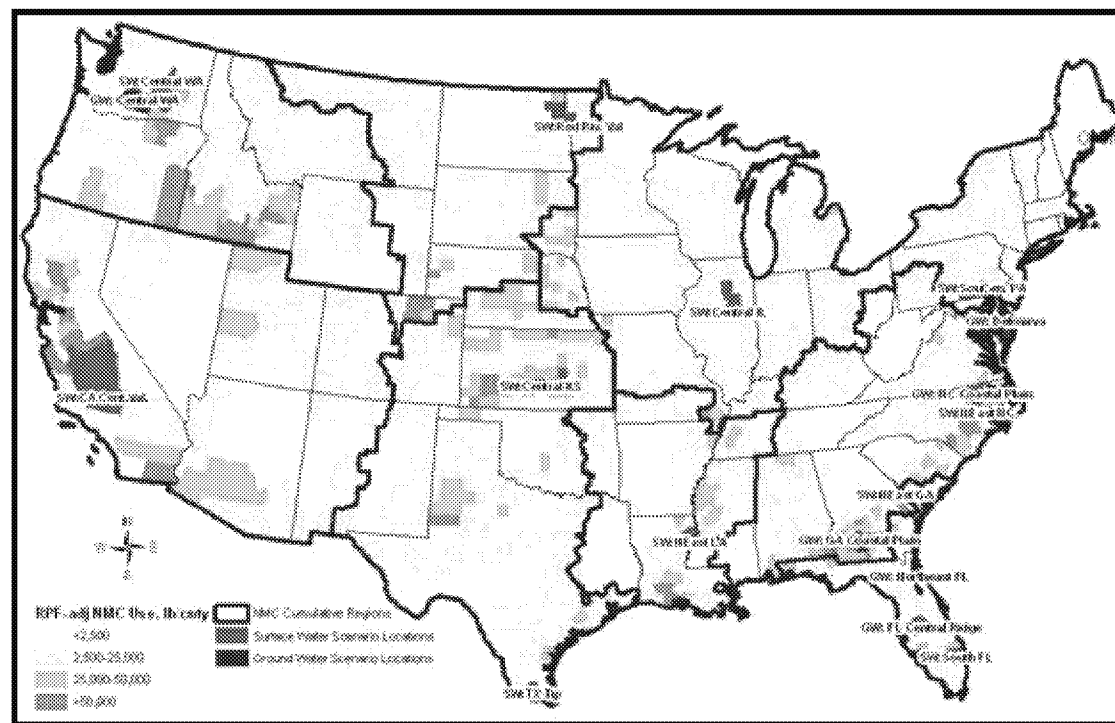
## Groups analyzed with 2016 screening framework - final

Group	Chemicals	Candidate CMG	Outcome
Chitin synthesis inhibitors	Buprofezin Cyromazine	No	Option 1: Conclusion of no common mechanism
Dinitroanilines	9 chemicals (butralin, benfluralin, etc)	No	Option 1: Conclusion of no common mechanism
Antibiotics	Streptomycin Kasugamycin Oxytetracycline	No	Option 1: Conclusion of no common mechanism
Acyl aminoacids	Benalaxyl Metalaxyl	No	Option 1: Conclusion of no common mechanism



# What if No Safety Finding can be Made with Screening Analysis?

- If the margin of exposure is not adequate following the initial screening analysis, more data and probabilistic analyses may be needed to increase refinement.



**NMC CRA regions for drinking water exposure assessment showing high NMC use areas and regional drinking water exposure sites**



# Current and Future Work on CRAs

- Alignment with Registration Review schedule (EPA 15-year review cycle for registered pesticides)
- Three additional groups being analyzed in 2019
- Recent publication on the use of ToxCAST data to support the identification of candidate CMGs



A weight of evidence approach to investigate potential common mechanisms in pesticide groups to support cumulative risk assessment: A case study with dinitroaniline pesticides

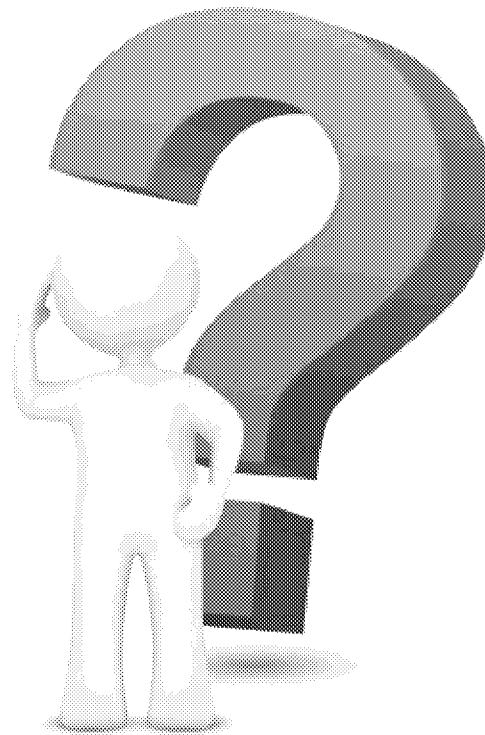


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## Summary

- Enough information is needed to establish a testable hypothesis for a candidate CMG in order to conduct cumulative risk assessments for pesticides in the US
- A tiered screening level approach is first applied to CRAs as a way to efficiently use resources
- If the margin of exposure is not adequate using the screening level approach, more data is required to perform full CRAs
- Pesticides must share a common mechanism of toxicity to be considered for assessing cumulative risk
- Grouping chemicals taking into account a common mechanism increases confidence in the cumulative assessment by risk managers



- <https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/pesticide-cumulative-risk-assessment-framework>